Overview of Outpatient Therapies Authorized for Mild to Moderate COVID-19



The table below summarizes important information about outpatient therapies currently authorized in the U.S. for treatment, pre-exposure and post-exposure prophylaxis of mild to moderate COVID-19. This table is similar in presentation to the Side-by-Side Overview table available in the U.S. Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response website¹. This table includes important information for providers specific to Utah, and it will be regularly reviewed and updated.

Please consult the Fact Sheets for Health Care Providers for each product regarding specific details (links provided below).

| Product | Sotrovimab Monoclonal Antibody | Tixagevimab and Cilgavimab (<u>Evusheld</u> ™) Monoclonal Antibodies | Ritonavir-Boosted Nirmatrelvir (<u>Paxlovid</u> ™) Antiviral | <u>Molnupiravir</u> Antiviral | Remdesivir (<u>Veklury</u> ®) Antiviral |
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| Manufacturer | GlaxoSmithKline | AstraZeneca | Pfizer | Merck Sharp & Dohme | Gilead |
| Mechanism of action | Monoclonal antibodies (mAbs) neutralize the spike protein to prevent viral attachment to host cells | Monoclonal antibodies (mAbs) neutralize the spike protein to prevent viral attachment to host cells | Protease inhibitor that blocks viral replication | Nucleoside analog that blocks viral replication via viral mutagenesis | RNA-dependent RNA polymerase inhibitor that blocks viral replication |
| Authorized use(s) per product Emergency Use Authorization (EUA)/ prescribing information | Per EUA: Treatment of lab-confirmed mild-moderate COVID-19 | Per EUA: Pre-exposure prophylaxis | P er EUA: Treatment of lab-confirmed mild-moderate COVID-19 | Per EUA: Treatment of lab-confirmed mild-moderate COVID-19 | Per Prescribing Information ² : Treatment of lab-confirmed mild-moderate COVID-19 in non-hospitalized patients Note: remdesivir is also FDA-approved for treatment of severe COVID-19 patients requiring hospitalization, however, criteria for hospitalized patients is beyond the scope of this document |
| Activity against SARS-Co-V-2 Variants of Concern (VOC): Delta and Omicron ^{3,4} | Delta variant: Active | Delta variant: Active | Delta variant: Active | Delta variant: Active | Delta variant: Active |
| | Omicron variant: likely active | Omicron: Active | Omicron: expected to be active | Omicron: expected to be active | Omicron: expected to be active |
| Eligible populations per product EUA/ prescribing information | Per EUA: ≥12 years old, and weighing ≥40 kg at high riskA for progressing to severe COVID-19, including hospitalization or death | Per EUA: patients ≥12 years old, and weighing ≥40 kg, who are not currently infected with SARS-Co-V-2 AND with additional eligibility criteriaB for Preexposure prophylaxis | Per EUA: patients ≥12 years old, and weighing ≥40 kg at high riskA for progressing to severe COVID-19, including hospitalization or death | Per EUA: adults ≥18 years old at high riskA for progressing to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options are not accessible or clinically appropriate | Per the PINETREE clinical trial ⁵ : patients ≥12 years old and weighing ≥40 kg, with at least one preexisting risk factorC for progression to severe COVID-19 OR were ≥60 years old, regardless of whether they had other risk factors |



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| Eligibility per UT COVID-19 Risk Score | Utah Crisis Standards of Care Scarce COVID Therapeutics Allocation Guidelines | Eligibility determined by tiered priority groups based on NIH guidance, the following tiers are eligible as of 1/21/2022 Phase I. Status: Active as of 12/28/2021 CAR-T recipient (2 years) Allogeneic stem cell transplant (2 years or on immunosuppression) Autologous stem cell transplant (1 year) Primary humoral immunodeficiency (CVID, etc.) B-cell depleting therapy in the last 6 months (monoclonal targets of CD19 or CD20) Other acquired or heritable hypogammaglobulinemia (IgG <600 mg/dL) B-cell malignancies (i.e. CLL, multiple myeloma) on active therapy or IVIG High-risk Solid organ transplant who were not fully vaccinated with mRNA series before transplant (3 doses of mRNA vaccine) Age ≥60; Lung recipient of any age HIV with CD4<200 Acute leukemia not fully vaccinated with mRNA series prior to starting treatment (3 doses of mRNA vaccine) Phase II. Status: Active as of 1/21/2022 All other Solid Organ transplant All other stem cell transplant and CAR-T Other hematologic malignancy receiving chemotherapy | Utah Crisis Standards of Care Scarce COVID Therapeutics Allocation Guidelines | Not in shortage, eligibility based on EUA and provider-patient determination Fact sheet for healthcare providers | To be determined. |
| Product availability in Utah | Extreme shortage – approximately 500- 550 a week available | Available through participating providers, approximately 600 a week allocated to Utah | Extreme shortage – approximately 340 a week available | Available through participating pharmacies, approximately 1,370 a week allocated to Utah | Not on Federal allocation, supplies available through healthcare facility acquisition and purchasing |



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| Limitations of authorized use | Not authorized for: Patients who are hospitalized due to COVID-19 Patients who require oxygen therapy due to COVID-19 OR Require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity) | Not authorized for: Treatment of COVID-19 OR Post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2 therapy due to COVID-19 Evusheld is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended Evusheld should be administered at least two weeks after COVID-19 vaccination | Not authorized for: Initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19 Pre-exposure or post-exposure prophylaxis for prevention of COVID-19 Use longer than 5 consecutive days | Not authorized for: Patients less than 18 years of age Initiation in patients who are hospitalized due to COVID-19 Use for longer than 5 consecutive days Pre-exposure or post-exposure prophylaxis for prevention of COVID-19 | Trial participants were ineligible for treatment if5: They were receiving or were expected to receive supplemental oxygen or hospital care They had a previous hospitalization for COVID-19 (including investigational agents) OR They had received a SARS-CoV-2 vaccine |
| Prescribing window | Treatment: within 10 days of symptom onset | Pre-exposure prophylaxis: Not specified | Treatment: within 5 days of symptom onset | Treatment: within 10 days of symptom onset | Treatment: within 7 days of symptom onset |
| Testing requirements | Treatment: Positive direct SARS-CoV-2 viral test | Pre-exposure prophylaxis: No testing required | Treatment: Positive direct SARS-CoV-2 viral test | Treatment: Positive direct SARS-CoV-2 viral test | Treatment: Positive direct SARS-CoV-2 viral test |
| Family planning considerations | No information available | No information available | Ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients should use an effective alternative contraceptive method or an additional barrier method of contraception | Molnupiravir not recommended in pregnancy, please see additional details^D below this table Females of reproductive potential: should use a reliable method of contraception correctly and consistently for the duration of treatment and for 4 days after the last dose of molnupiravir Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose | No information available |
| Contraindications | Patients who have a history of anaphylaxis to sotrovimab or to any of the excipients in the formulation | Individuals with previous severe hypersensitivity reaction, including anaphylaxis, to Evusheld | Individuals with significant hypersensitivity reactions to any component of Paxlovid Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or lifethreatening reactions Co-administration with potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response | None per current EUA | Hypersensitivity to remdesivir or any component of the formulation |



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| Administration route(s) | IV | IM | Oral | Oral | IV |
| Dosage | 500 mg single infusion following dilution | Initial and Repeat dose: 150 mg of tixagevimab and 150 mg of cilgavimab administered as two separate consecutive intramuscular (IM) injections Of note: Per the conditions in the Evusheld EUA, it can be redosed every 6 months, however, there are no safety and efficacy data available for repeat dosing | 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all three tablets taken together orally twice daily for 5 days, can be taken with or without food [see Clinical Pharmacology (12.3)]. The tablets should be swallowed whole and not chewed, broken, or crushed. For patients with renal impairment, see below | 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. | 200 mg as single dose on day 1, followed by 100 mg once daily on days 2 and 3 Note: dosing for remdesivir varies by indication, the dosing provided above is for Treatment of lab-confirmed mild-moderate COVID-19 in non-hospitalized patients |
| Dosage for special populations | Hepatic: not specified No dosage adjustment recommended in other special populations (eligible pediatrics, pregnancy/lactation, renal) | No dosage adjustment recommended in special populations (pregnancy/lactation, geriatrics, renal) | No dose adjustment is needed in patients with mild renal impairment Dose reduction for moderate renal impairment (eGFR ≥30 to <60 ml/min): 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days Not recommended in patients with severe renal impairment (eGFR <30 ml/min) No dosage adjustment recommended in other special populations (pregnancy/lactation, eligible pediatrics, hepaticin patients with mild to moderate hepatic impairment). Paxlovid is not recommended in patients with severe hepatic impairment. | Pediatrics: Not eligible, as it may affect bone and cartilage growth Pregnancy or Lactation: Not recommended for use during pregnancy. Breastfeeding not recommended during treatment or for 4 days after final dose No dosage adjustment recommended in other special populations (hepatic, renal) | Renal: eGFR ≥30 ml/min: no dosage adjustment necessary eGFR <30: use not recommended Hepatic: No dosage adjustments provided for baseline hepatic impairment |
| Post-administration observation period | Clinically monitor patients after injection and observe patients for at least 1 hour after intravenous infusion, or intramuscular injection | Clinically monitor patients after injections and observe patients for at least 1 hour after intramuscular injections | None | None | Clinically monitor patients after injection and observe patients for at least 1 hour after intravenous infusion |



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| Warnings and precautions | Hypersensitivity including anaphylaxis and infusion-related reactions Clinical worsening after sotrovimab administration Sotrovimab may be associated with worse clinical outcomes when administered to hospitalized patients | Hypersensitivity including anaphylaxis Evusheld should be given with caution to individuals with clinically significant bleeding disorders given its IM route of administration A higher proportion of patients who received Evusheld reported myocardial infarction and cardiac failure serious adverse events, a causal relationship between Evusheld and these events has not been established | Risk of serious adverse reactions due to drug-drug interactions: refer to table 1 of the Paxlovid Fact Sheet for Healthcare Providers for clinically significant drug-drug interactions Risk of hepatotoxicity (transaminase elevations, clinical hepatitis, and jaundice) with ritonavir Risk of HIV-1 resistance development in patients with uncontrolled or undiagnosed HIV-1 infection taking Paxlovid | Embryo-Fetal Toxicity: please refer to the "Family Planning Considerations" section above Bone and Cartilage Toxicity: molnupiravir is not authorized for use in patients younger than 18 years of age because it may interfere with bone and cartilage growth | Hypersensitivity including anaphylaxis Increased risk of transaminase elevations. Perform hepatic laboratory testing in all patients before starting remdesivir and consider discontinuing treatment if: ALT increases > 10 times ULN or if ALT elevation is accompanied by signs and symptoms of liver inflammation Risk of reduced antiviral activity when coadministered with chloroquine phosphate or hydroxychloroquine sulfate |
| Adverse events | Infusion-related reactions (1%); One case of anaphylaxis, pyrexia, chills, dizziness, dyspnea | Headache, fatigue, cough; one case of anaphylaxis; higher rate of cardiovascular serious adverse events, including one death from myocardial infarction in a patient on Evusheld (per the PROVENT trial) | Adverse events (incidence ≥1% and ≥ 5 patient difference): dysgeusia (6%), diarrhea (3%), hypertension (1%), and myalgia (1%) | Adverse events (incidence ≥1%): diarrhea (2%), nausea (1%), dizziness (1%) | Most common adverse effects: nausea (10.8%), headache (5.7%), and cough (3.6%) |
| Potential for drug-drug-interactions Liverpool COVID-19 Drug Interactions Checker | Not renally excreted or metabolized by cytochrome P450 enzymes, thus, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 are unlikely | Not renally excreted or metabolized by cytochrome P450 enzymes, thus, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 are unlikely | Moderate/High [see Fact Sheet for healthcare providers: Drug Interactions Section (7) at the link below] | No drug interactions have been identified based on the limited available data | Medications to avoid concomitant use: chloroquine and hydroxychloroquine may diminish the therapeutic effect of remdesivir Monitor therapy: Strong CYP3A4 Inducers may decrease the serum concentration of remdesivir |
| Considerations | Infusion/injection supplies; trained staff, IV access, immediate access to resuscitation meds; ability to activate EMS | Consider the risks and benefits prior to initiating Evusheld in individuals at high risk for cardiovascular events | Paxlovid is the treatment with the greatest risk of drug-drug interactions, and it is dosage depends on the severity of renal impairment | Molnupiravir is an agent of last resort given its lower efficacy compared to other treatments and its potential for adverse effects/toxicity ⁶ | Infusion/injection supplies; trained staff, IV access, immediate access to resuscitation meds; ability to activate EMS |
| FDA required fact sheets | Healthcare providers Patients and caregivers (English, Spanish) | Healthcare providers Patients and caregivers (English) | Healthcare providers Patients and caregivers (English, Spanish) | Healthcare providers Patients and caregivers (English, Spanish) | Healthcare providers Patients and caregivers (English, Spanish) |



APlease consult each product's Fact Sheet for Healthcare Providers for additional details and criteria for identifying high risk patients/individuals. Another resource for medical conditions that increase the risk of severe COVID-19 is maintained by the CDC.

Eligibility for pre-exposure prophylaxis: individuals not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2, AND who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments AND may not mount an adequate immune response to COVID-19 vaccination, OR for who vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

^cPreexisting risk factors for progression to severe COVID-19 per the PINETREE clinical trial: hypertension, cardiovascular or cerebrovascular o chronic lung disease, current cancer, or sickle cell disease.

Per the Molupiravir EUA: This product is not recommended for use during pregnancy due to a risk of fetal harm when given to pregnancy only if benefits would outweigh risks for the individual patient; and there are a number of documentation requirements. Please refer to molnupiravir's Fact Sheet for Healthcare Provided above) for details regarding specific documentation requirements.

Per The COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-196:

- Favored Treatment: Ritonavir-Boosted Nirmatrelvir (Paxlovid)
 - Rationale: Paxlovid has been shown to have comparable efficacy to sotrovimab and remdesivir at reducing the relative risk of hospitalization or death (88% reduction) compared to placebo in nonhospitalized patients with mild to moderate COVID-19, and it is expected to be active against the Omicron VOC
- If Paxlovid unavailable or cannot be used due to drug interactions: use Sotrovimab
 - Rationale: Sotrovimab has been shown to reduce the relative risk of hospitalization or death compared to placebo in nonhospitalized patients with mild to moderate COVID-19 by 79%. In vitro studies indicate that sotrovimab is active against Omicron VOC
- If Sotorvimab is not available: use Remdesivir off-label
 - Rationale: Remdesivir has been shown to reduce the relative risk of hospitalization or death compared to placebo in nonhospitalized patients with mild to moderate COVID-19 by 87%. However, it requires IV infusion for 3 consecutive days, which poses a greater administration barrier compared to sotrovimab. Remdesivir is also expected to be active against Omicron VOC
- Molnupiravir should only be used when the three options above are either not available or cannot be used
 - Rationale: Molnupiravir has lower efficacy compared to the three options above (30% relative risk reduction of the rate of hospitalization or death), and it is also expected to be active against Omicron VOC

References:

- 1. U.S. Department of Health and Human Services: Office of the Assistant Secretary for Preparedness and Response. Side-by-Side Overview of Outpatient Therapies Authorized for Treatment of Mild-Moderate COVID-19. 12/31/2021. Author. https://www.phe.gov/ emergency/events/COVID19/therapeutics/Pages/Side-by-Side-Overview-of-mAbs-Treatment.aspx
- 2. Prescribing Information for Veklury. 1/21/2022. https://www.accessdata.fda.gov/drugsatfda docs/label/2022/214787Orig1s010Lbl.pdf
- 3. The COVID-19 Treatment Guidelines Panel. The COVID-19 Treatment Guidelines Panel's Statement on the Use of Anti-SARS-CoV-2 Monoclonal Antibodies or Remdesivir for the Treatment of COVID-19 in Nonhospitalized Patients When Omicron Is the Predominant Circulating Variant. 12/23/2021. Author. statement-on-anti-sars-cov-2--12-23-2021.pdf (nih.gov)
- 4. AstraZeneca. Evusheld long-acting antibody combination retains neutralizing activity against Omicron variant in studies from Oxford and Washington Universities. 12/23/2021. Author. https://www.astrazeneca.com/media-centre/press-releases/2021/evusheld-long-activity against Omicron variant in studies from Oxford and Washington Universities. acting-antibody-combination-retains-neutralising-activity-against-omicron-variant-in-studies-from-oxford-and-washington-universities.html
- 5. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe COVID-19 in Outpatients. N Engl J Med 2021. DOI: 10.1056/NEJMoa2116846.
- 6. The COVID-19 Treatment Guidelines Panel. The COVID-19 Treatment Guidelines Panel. The COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Nonhospitalized Patients | COVID-19 Treatment Guidelines (nih.gov)

